Practitioner's Docket No. 0055.00 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Schutt et al.
Application No.: 09/218,213 Group No.: 1615
Filed: 12/22/1998 Examiner: S. Tran
For: STABILIZED PREPARATIONS FOR USE IN NEBULIZERS

Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF APPEAL BRIEF (PATENT APPLICATION--37 C.F.R. 1.192)

1. Transmitted herewith, in triplicate, is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on May 15, 2001.

2. STATUS OF APPLICANT

This application is on behalf of other than a small entity.

3. FEE FOR FILING APPEAL BRIEF

Pursuant to 37 C.F.R. 1.17(c), the fee for filing the Appeal Brief is:

Other than a small entity	$320.00
Appeal Brief fee due	$ 320.00

CERTIFICATE OF MAILING/TRANSMISSION (37 C.F.R. 1.8(a))

I hereby certify that, on the date shown below, this correspondence is being:

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☒ deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: 11/15/01

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Kathy Honnert
Signature

Kathy Honnert
(type or print name of person certifying)

4. EXTENSION OF TERM

The proceedings herein are for a patent application and the provisions of 37 C.F.R.section 1.136 apply.

Applicant petitions for an extension of time under 37 C.F.R. 1.136 (fees: 37 C.F.R. section 1.17(a)(1)-(5)) for four months:

Fee	$ 1,440.00

If an additional extension of time is required, please consider this a petition therefor.

5. TOTAL FEE DUE

The total fee due is:

Appeal brief fee	$ 320.00
Extension fee (if any)	$1,440.00
TOTAL FEE DUE	**$ 1,760.00**

6. FEE PAYMENT

Charge Account No. 500348 the sum of $ 1,760.00
A duplicate of this transmittal is attached.

7. FEE DEFICIENCY

If any additional extension and/or fee is required, this is a request therefor and to charge Account No. 500348. If any additional fee for claims is required, charge Account No. 500348.

Date: 11/15/01

Signature of Practitioner

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29/ Ext time (4 mos) + Appeal Brief (3) 11-15-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant	:	Schutt et al.	Group Art Unit 1615
Appl. No.	:	09/218,213	
Filed	:	December 22, 1998	
For	:	STABILIZED PREPARATIONS FOR USE IN NEBULIZERS	
Examiner	:	TRAN, S.	

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11/15/01 (Date)

Kathy Honnert 11-25-92

Kathy Honnert

APPELLANT'S BRIEF UNDER 37 C.F.R. §1.192

Assistant Commissioner for Patents

Washington D.C. 20231

Sir:

Enclosed is Appellant's Brief filed under 37 C.F.R. §1.192 in response to the Final Office Action mailed November 16, 2001. A Notice of Appeal was filed on May 15, 2001. This Appellant's Brief is accompanied by a Fee Authorization and Petition to extend the time for response 4 months from July 15, 2001 to November 15, 2001.

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01 FC:120 320.00 CH

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I. Real Party in Interest

The real party in interest is Inhale Therapeutic Systems, Inc. 150 Industrial Road, San Carlos, California 94070.

II. Related Appeals and Interferences

Appellant is not aware of other appeals or any interferences related to the above captioned application.

III. Status of Claims

Claims 2, 6-12, 39, and 43-55 are pending in the above-captioned application and are subject of this appeal. No claim is allowed. Claims 1, 3-5, 13-38, and 40-42 have been cancelled. A copy of the pending claims is attached hereto.

IV. Status of Amendments

An After Final Amendment was filed February 26, 2001 and has not been entered.

An After Final Amendment filed March 28, 2001 has been filed and has been entered according to the Advisory Action of June 29, 2001.

V. Summary of Invention

The present invention relates to methods and systems for administering stabilized dispersions via nebulization to the respiratory tract. Nebulizers work by forming aerosols by converting bulk liquid into small droplets suspended in a breathable gas. The bulk liquid or respiratory dispersion in the case of the present invention is a particulate suspension of perforated microstructures suspended in a fluorochemical suspension medium. Unlike prior art

formulations, the present invention employs novel techniques to reduce attractive forces between the dispersed constituents and to reduce density fluctuations in the stabilized dispersion thereby retarding degradation of the preparation by flocculation, sedimentation, or creaming. The stable dispersion of the present invention thereby reduces dosing incongruities thereby facilitating drug delivery.

The claims find support throughout the specification. For example, claims 2 and 39 find support at page 6, lines 11-23, page 7, line 28 – page 9, line 11, and page 17, line 23 – page 18, line 11; claims 6, 47 and 54 at page 21, lines 5-16 and page 23, lines 1-14; claims 7-10 and 43-46 at page 25, line 7 – page 26, line 20; claims 11, 48, 49, and 55 at page 9, line 21 – page 10, line 8 and page 30, line 3 – page 31, line 6; claim 12 at page 45, lines 17-24; claims 50 and 51 at page 45, line 25 – page 48, line 29; and claims 52 and 53 at page 21, line 17 – page 22, line 7.

VI. Issues

Are claims 2, 6-12, 39, and 43-55 patentable in view of Faithful et al. (6,041,777) further in view of Hanes et al. (5,855,913)?

VII. Grouping of Claims

Claims 2 and 6-12 stand or fall together. These claims are directed to a method of administering stabilized dispersions comprising one or more bioactive agents wherein the respiratory dispersion comprises a plurality of perforated microstructures suspended in and substantially permeated by a fluorochemical continuous phase wherein the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure.

Claims 39 and 43-55 stand or fall together. These claims are directed to a system for administering such stabilized dispersions.

VIII. Argument

Claims 2, 6-12, 39, and 43-55 have been rejected under 35 U.S.C. § 103 as being unpatentable over Faithfull et al. in view of Hanes et al.

As Appellant's understand it, the Examiner's position may be concisely summarized as follows[1]:

Faithfull et al. teaches methods and apparatus for closed-circuit ventilation for pulmonary administration of fluorochemical agents and pharmaceutical agents. Such liquid ventilation may further include a nebulizer for introducing an aerosol, mist, or spray to deliver a respiratory promoter or bioactive agent to the gas flow path. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the liquid ventilation process and system of Faithfull et al. with the use of a phospholipid surfactant in view of such teachings in Hanes et al. in order to improve the aerosolization of the particles, reduce agglomeration, and thus promote absorption of a drug and increase bioavailability of the drug in the lung.

For the reasons discussed *infra*, Appellants respectfully submit the Examiner has failed to establish a *prima facie* case of obviousness and that the pending claims are patentable in view of the cited art. As the Board is aware, to establish that a claimed invention is *prima facie* obvious over the prior art, it must be established that the prior art would have suggested to one of ordinary skill in the art that they carry out the claimed process, and that in so doing those of ordinary skill in the art would have had a reasonable expectation of success. *In re Vaeck*; 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Appellants will first describe the cited references individually and then will consider the combinations and reasoning asserted by the Examiner.

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[1] The basis for this summary is the Examiner's comments in the Final Office Action dated November 16, 2000. It is believed that that Examiner's statement in the Advisory Action of June 29, 2001 in which the After Final Amendment filed was to be entered reflects that the rejection under 35 U.S.C. §112, first paragraph of claims 2 and 39 as set forth in the Final Rejection of November 16, 2000 has been withdrawn.

A. The Cited References

1. Faithfull et al.

Faithfull et al. is directed to an apparatus and method for closed circuit ventilation therapy. As disclosed at column 16, lines 27-55, the ventilation system may further comprise a nebulizer 98 communicating with the inspiratory ventilating conduit 50. The nebulizer may be used to deliver liquid medium such as fluorochemicals heated above body temperature to the ventilating gas in the form of a vapor to assist in gas exchange and oxygenation. As seen at column 17, lines 5-29, Faithfull et al. teaches performing partial liquid ventilation (PLV) comprising the administration of very low doses of fluorochemicals (0.01 ml/kg or less) sufficient to form a thin coating on a portion of the lung to reduce surface tension at the alveolar air-liquid interface thereby facilitating lung expansion and increasing oxygen availability. Alternatively, Faithfull et al. suggests the use of a nebulizer to administer fluorochemical or respiratory agents to the gas flow path for the closed-circuit ventilation system (22: 26-35, 23: 35-42). Faithfull et al. discloses fluorochemicals as a respiratory promoter (defined at column 4, lines 2-5 as agents that improve gas exchange and respiratory efficiency) and liquid breathing agents to be administered to a patient.

2. Hanes et al.

Hanes et al. is directed to porous particles for aerosol drug delivery. As seen throughout Hanes et al., the invention is directed to large (main diameter of 5-30 microns, light (tap density less than 0.4 g/cm^3) particles for aerosol delivery. The particles disclosed in Hanes et al. are directed to aerosol delivery as a dry powder. The rough surface texture to reduce particle aggregation and improve flowability of the powder as cited in Hanes et al. 4:53-56 relates to properties and characteristics of dry powders administered as aerosols.

B. None of the Cited References, Either Individually or in Combination, Would Have Rendered the Claimed Invention Obvious Under 35 U.S.C. §103(a).

Appellants respectfully submit the Examiner has failed to establish a proper *prima facie* case of obviousness and that the pending claims are patentable in view of the cited art.

3. No combination of references suggested the claimed respiratory dispersion comprising particles suspended in a flurochemical suspension medium

Claims 2 and 39 are directed to a method and system, respectively, for administering a stabilized respiratory dispersion via nebulization, which dispersion comprise a plurality of perforated microstructures[2] suspended in and substantially permeated by a fluorochemical continuous phase. The claims further provide that the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure. These claims stand rejected in view of Faithfull et al. and Hanes et al.

Faithfull et al. is directed to a sophisticated ventilation system for closed-circuit ventilation therapy. As part of that system, Faithfull et al. suggests that drug administration to the respiratory tract can be concurrently performed. For example, Faithfull et al. discloses at column 25, lines 15-30 that the invention may be used to deliver pharmaceutical agents in conjunction with ventilation. In this respect, one of ordinary skill in the art would understand this disclosure to refer to administering a drug in the perflurochemical liquid which is directly instilled in the patient's respiratory tract. Such administration is not related to and in no way suggests respiratory dispersions for nebulization as claimed.

As a separate means to deliver drugs concurrently with the ventilation system, Faithfull et al. discloses that a nebulizer can be fed into the gas stream of the ventilator system. The nebulizer can administer a liquid fluorochemical alone, or may administer a bioactive agent (16: 41-46, 22:28-30). Faithfull et al does not disclose or suggest the use of a fluorochemical as a suspension medium for a respiratory dispersion to be administered via nebulization. In particular, Faithfull et al. does not provide any guidance whatsoever as to respiratory suspensions

[2] The term "perforated microstructure" is defined at page 6, lines 11-23 as comprising "...pores, voids, defects, or other interstitial spaces that allow the fluid suspension medium to freely permeate, or perfuse, the particle boundary...".

to be administered via nebulization and is silent as to stability problems associated with suspensions for nebulization.

The Examiner has relied upon Hanes et al. to satisfy these deficiencies. In particular, the Examiner has stated that it would have been obvious to modify the Faithfull et al. system to include phospholipids disclosed in Hanes et al. in order to stabilize and improve aerosol characteristics of the liquid ventilation system of Faithfull et al.

The proposed combination lacks any suggestion to suspend the Hanes et al. particles in a fluorochemical suspension medium for administration via nebulization methods and systems as claimed. Neither references suggests the use of a fluorochemical as a suspension medium for respiratory dispersions to be administered via nebulization. One of ordinary skill would not be motivated to make the combination to arrive at the present invention without the aid of impermissible hindsight

Recently, the Federal Circuit has held that the mere identification of prior art statements that, in the abstract, appear to suggest the claimed limitation does not establish a *prima facie* case of obviousness without a finding as to the specific understanding or principle within the knowledge of one of skill in the art that would have motivated one with no knowledge of the invention to make the combination in the manner claimed. *In re Kotzab*, 55 USPQ 2d 1313 (Fed. Cir. 2000). The cited references are silent as to suspension stability of dispersions to be administered via nebulization and in no way disclose or suggest the unique approach of the claimed invention wherein particle morphology of perforated microstructures is controlled in order to provide stable suspensions in a fluorochemical medium for methods and systems for administration via nebulization. Nothing in the art suggested that perforated microstructures suspended in a fluorochemical suspension medium results in stable suspensions for nebulization which resist degradation, flocculation, sedimentation, and creaming in order to provide improved consistency in aerosol administration via nebulization.

2. Even combining Faithful et al. and Hanes et al. would not have led to the claimed invention

Even if, *arguendo*, one of skill had attempted to "combine" the references as suggested by the Examiner, the resultant combination would not have led to the claimed invention. None of

the references suggested providing a suspension of perforated microstructures in a suspension medium wherein the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure as recited in claims 2 and 39 in order to provide methods and systems for nebulization.

3. Nothing in the prior art would have provided an expectation of success for the claimed method and system

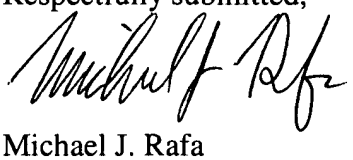
A showing of *prima facie* obviousness also requires that the references relied upon provide a reasonable expectation of success when combined in the manner relied upon in the rejection. Not only must the prior art suggest the claimed invention, but also the combination must provide "a reasonable expectation of success viewed in light of the prior art". *Amgen v. Chugai*, 18 U.S.P.Q.2 nd 1016-1022 (Fed. Cir. 1991). "Both the suggestion and the expectation of success must be found in the prior art, not the patentee's disclosure." *Id., citing in re Dow Chemical Company*, 5 U.S.P.Q. 2 nd 1593, 1597 (Fed. Cir. 1988). Even if, *arguendo*, one had attempted to combine the Hanes et al. particles with a fluorochemical medium to provide a suspension for nebulization, nothing in the prior art would have provided a reasonable expectation of success in carrying out the claimed invention. Nothing in the art suggested that perforated microstructures suspended in fluorochemical suspension medium results in stable suspensions for nebulization which resist degradation, flocculation, sedimentation, and creaming in order to provide improved consistency in methods and systems for aerosol administration via nebulization.

IX. Conclusions

Appellants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness of the claims that are presented on appeal. None of the cited references, individually or in combination, describe or suggest the methods and systems

of the present invention. Accordingly, Appellants respectfully request that the Board reverse the Examiner's rejection of the claims on appeal.

Respectfully submitted,



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X. Appendix

Claims Under Appeal

2. A method for the pulmonary delivery of one or more bioactive agents comprising the steps of:

providing a stabilized respiratory dispersion comprising one or more bioactive agents wherein the respiratory dispersion comprises a plurality of perforated microstructures suspended in and substantially permeated by a fluorochemical continuous phase wherein the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure;

mobilizing said respiratory dispersion with a nebulizer to provide an aerosolized medicament; and

administering a therapeutically effective amount of said aerosolized medicament to at least a portion of the pulmonary passages of a patient in need thereof.

6. The method of claim 2 wherein the mean aerodynamic diameter of the perforated microstructures is between 0.5 and 5μm.

7. The method of claim 2 wherein said perforated microstructures comprise a surfactant.

8. The method of claim 7 wherein said surfactant is selected from the group consisting of phospholipids, nonionic detergents, nonionic-block copolymers, ionic surfactants, biocompatible fluorinated surfactants and combinations thereof.

9. The method of claim 7 wherein said surfactant is a phospholipid.

10. The method of claim 9 wherein said phospholipid is selected from the group consisting of dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine,

disteroylphosphatidylcholine, behenoylphosphatidylcholine, arachidoylphosphatidylcholine and combinations thereof.

11. The method of claim 2 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary lung surfactants, analgesics, antibiotics, leukotriene inhibitors or antagonists, antihistamines, antiinflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

12. The method of claim 2 wherein said bioactive agent is delivered to the systemic circulation of said patient.

39. An inhalation system for the pulmonary administration of a bioactive agent to a patient comprising:

a fluid reservoir;

a stable respiratory dispersion in said fluid reservoir wherein said stabilized dispersion comprises a fluorochemical continuous phase and a plurality of perforated microstructures comprising at least one bioactive agent suspended in and substantially permeated by the continuous phase wherein the volume of suspension medium displaced by the perforated microstructure is less than 70% of the average particle volume of the perforated microstructure; and

a nebulizer operably associated with said fluid reservoir wherein the nebulizer is capable of aerosolizing and discharging the stable respiratory dispersion.

43. The system of claim 39 wherein said perforated microstructures comprise a surfactant.

44. The system of claim 43 wherein said surfactant is selected from the group consisting of phospholipids, nonionic detergents, nonionic block copolymers, ionic surfactants, biocompatible fluorinated surfactants and combinations thereof.

45. The system of claim 43 wherein said surfactant is a phospholipid.

46. The system of claim 45 wherein said phospholipid is selected from the group consisting of dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, behenoylphosphatidylcholine, arachidoylphosphatidylcholine and combinations thereof.

47. The system of claim 39 wherein the mean aerodynamic diameter of the perforated microstructures is between 0.5 and 5μm.

48. The system of claim 39 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary lung surfactants, analgesics, antibiotics, antiinfectives, leukotriene inhibitors or antagonists, antihistamine, antiinflammatories, antineoplastics, antocholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzyme, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

49. The system of claim 39 wherein said bioactive agent comprises a compound selected from the group consisting of proteins, peptides and genetic material.

50. The system of claim 39 wherein said fluid reservoir is a multi-dose reservoir or a single dose reservoir.

51. The system of claim 39 wherein said nebulizer is a jet nebulizer, an ultrasonic nebulizer or a single-bolus nebulizer.

52. The system of claim 39 wherein the respiratory dispersion comprises a creaming time of greater than 1 minute.

53. The system of claim 39 wherein the respiratory dispersion comprises a creaming time of greater than 30 minutes.

54. The system of claim 39 wherein the perforated microstructures comprise a geometric diameter of 1-30μm.

55. The system of claim 48 wherein the bioactive agent is an antiinfective selected from the group consisting of cephalosporines, macrolides, quinoline, penicillins, streptomycin, sulphonamides, tetracyclines, and pentamidine.

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The following papers listed below are submitted:

Appeal Brief Transmittal
Appeal Brief (in triplicate)